DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Carol Childers
Director
Teva Neuroscience, Inc.
901 East 104th Street, Suite 900
Kansas City, MO 64131

RE: ANDA 076809
Clozapine tablets USP
MA# 44

Dear Ms. Childers:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed an article detailer (1080101/121962) for Clozapine tablets USP (clozapine) submitted by Teva Neuroscience, Inc. (Teva) under cover of Form FDA 2253. The article detailer is misleading because it makes unsubstantiated superiority and other claims regarding clozapine, omits material facts, and minimizes the risks associated with the drug. The article detailer, therefore, misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), 21 U.S.C. 352(a) & 321(n), and FDA implementing regulation 21 CFR 1.21(a). *Cf.* 21 CFR 202.1(e)(5)(i), (iii); (e)(6)(i), (ii); (e)(7)(i), (iii), (viii).

Background

Below is the indication and summary of the most serious and most common risks associated with the use of clozapine[1]. According to the INDICATIONS AND USAGE section of the FDA-approved product labeling (PI) (in pertinent part):

> **Treatment-Resistant Schizophrenia**
> Clozapine is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard drug treatment for schizophrenia. Because of the significant risk of agranulocytosis and seizure associated with its use, clozapine should be used only in patients who have failed to respond adequately to treatment with appropriate courses of standard drug treatments for schizophrenia, either because of insufficient effectiveness or the inability to achieve an effective dose due to intolerable adverse effects from those drugs.
> . . .

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece(s) cited in this letter.

Reduction in the Risk of Recurrent Suicidal Behavior in Schizophrenia or Schizoaffective Disorders

Clozapine is indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at chronic risk for re-experiencing suicidal behavior, based on history and recent clinical state. Suicidal behavior refers to actions by a patient that puts him/herself at risk for death.

. . .

Clozapine is associated with a number of serious risks, many of which are potentially fatal, including Boxed Warnings for potentially fatal agranulocytosis, seizures, myocarditis, other adverse cardiovascular and respiratory effects, and increased mortality in elderly patients with dementia-related psychosis. Clozapine is contraindicated in patients with a previous hypersensitivity to clozapine or any other component of this drug; in patients with myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, or a history of clozapine-induced agranulocytosis or severe granulocytopenia; and in severe central nervous system (CNS) depression or comatose states from any cause. Furthermore, clozapine should not be used simultaneously with other agents having a well-known potential to cause agranulocytosis or otherwise suppress bone marrow function. The PI also contains Warnings regarding eosinophilia; QT interval prolongation; neuroleptic malignant syndrome (NMS); tardive dyskinesia (TD); and hyperglycemia and diabetes mellitus. In addition, the PI includes Precautions regarding, among other things, avoiding extended treatment in patients failing to show an acceptable level of clinical response and to periodically re-evaluate the need for continuing treatment in patients exhibiting beneficial clinical responses; cardiomyopathy; fever; pulmonary embolism; phenylketonurics; hepatitis; anticholinergic toxicity associated with the eye, gastrointestinal (GI) system, and prostate; and interference with cognitive and motor performance.

As stated in the PI, clozapine is associated with the following common adverse reactions (incidence of greater than 5%): CNS complaints, including drowsiness/sedation, dizziness/vertigo, headache, and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth, and visual disturbances; cardiovascular findings, including tachycardia, hypotension, and syncope; GI complaints, including constipation and nausea; and fever.

Unsubstantiated Claims/Unsubstantiated Superiority Claim

Promotional materials are misleading if they contain representations that the drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. Promotional materials are also misleading if they contain representations or suggestions that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience.

Page one[2] of the article detailer includes the following claims (emphasis original):

> "Treatment with the three atypical agents studied (clozapine, olanzapine, and risperidone) was associated with significant improvements in 3 of 5 PANSS symptom clusters (positive, cognitive, depression/anxiety). Clozapine and olanzapine showed improvement in the negative cluster.
>
> **Only clozapine was associated with significant improvement in the excitement symptom cluster.**"

Page two of the article detailer contains the following claim and presentation (emphasis original):

- "The study authors determined that hostility, excitement, uncooperativeness, and poor impulse control – the symptoms comprising the 'excitement cluster' – reflected a predominance of behavioral dyscontrol syndrome at baseline"
- Graphic presentation of the following four symptoms that are included in the "**EXCITEMENT**" symptom cluster: "**EXCITEMENT**", "**HOSTILITY**", "**POOR IMPULSE CONTROL**", and "**UNCOOPERATIVENESS**" under the header, "**Discussion of 'Excitement Factor' Symptoms as an Indicator of Poor Prior Antipsychotic Response**"

In addition, page three of the article detailer includes a comparative graphic presentation which details the results of the five-factor analysis (excitement, positive, negative, cognitive, and depression/anxiety components) for clozapine, olanzapine, risperidone, and haloperidol. Specifically, the graphic presentation visually describes the data for each symptom cluster with regards to each of the four drugs studied using different colors for the following outcomes: "**SIGNIFICANT IMPROVEMENT**," "**NO SIGNIFICANT CHANGE**," and "**SIGNIFICANTLY WORSENED**" (emphasis original). The graphic presentation is presented in direct conjunction with the following claims (emphasis original):

- "Both clozapine and olanzapine improved the *negative* symptom cluster in a similar manner"
- "Clozapine, olanzapine, and risperidone all significantly improved the *positive, cognitive*, and *depression/anxiety* symptom clusters"

Page three also includes the following claims under the heading "**Investigator's comments**" (emphasis original; footnote omitted), located directly below the graphic presentation described above (emphasis original):

- "**'It was remarkable that even in patients with prior treatment resistance, we were able to demonstrate effects by all three atypical antipsychotics in the cognitive and depression/anxiety domains. . .'**"
- "**The excitement domain findings of this study 'further point to clozapine's efficacy for patients having difficulty with aggression and impulse control.'**"

[2] Please note that for the purpose of this letter, we have numbered the pages in the article detailer, one through four, accordingly, with page one representing the front cover of the article detailer, page two representing the second page of the article detailer, and so on.

The above claims and presentations are misleading because they imply that clozapine demonstrated significant efficacy in treating four of the five "symptom clusters" associated with schizophrenia – excitement, positive, cognitive, and depression/anxiety, as well as specific symptoms of excitement, when this has not been demonstrated by substantial evidence or substantial clinical experience. The study[3] described in the article detailer in support of these claims and presentations presents the results of a retrospective Positive and Negative Syndrome Scale (PANSS)-derived five-factor analysis of data from a previously conducted "prospective, double-blind, randomized 14-week trial[4]." However, a single, retrospective, PANSS-derived five-factor analysis on data obtained from a previously published study does not constitute substantial evidence or substantial clinical experience to support such claims and presentations. Therefore, the cited study does not constitute substantial evidence or substantial clinical experience to support efficacy claims and presentations regarding specific symptom clusters or specific symptoms associated with schizophrenia.

Furthermore, the claims, "Clozapine was superior to both risperidone and haloperidol in treating the *excitement* cluster (in a post-hoc analysis)" and "**'Only clozapine was associated with improvement in the excitement domain'**" (emphasis original), in conjunction with the comparative graphic presentation detailing the results of the PANSS-derived five factor analysis, misleadingly suggest that clozapine is superior to the other drugs studied (olanzapine, risperidone, and haloperidol) based on clozapine's purported improvement in the excitement symptom cluster. These claims, however, are not supported by substantial evidence or substantial clinical experience. Generally, claims of superiority must be supported by two adequate and well-controlled head-to-head clinical trials comparing appropriate doses and dose regimens of your drug and the comparator drug(s). A single, retrospective analysis[3] of a previously conducted clinical study[4] would not be considered substantial evidence or substantial clinical experience to support the implication of superiority for clozapine.

Omission of Material Fact/Minimization of Risk

Promotional materials are misleading if they fail to reveal material facts in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. Specifically, the article detailer fails to disclose that clozapine is contraindicated in patients with a previous hypersensitivity to clozapine or any other component of the drug. Furthermore, the article detailer also omits material information from a number of risks associated with clozapine, including QT interval prolongation, hyperglycemia and diabetes mellitus, NMS, TD, cardiomyopathy, fever, pulmonary embolism, hepatitis, anticholinergic toxicity, and interference with cognitive and motor performance. For example, while the article detailer includes limited information regarding QT interval prolongation associated with clozapine, it

[3] Lindenmayer JP, Czobor P, Volavka J, et al. Effects of Atypical Antipsychotics on the Syndromal Profile in Treatment-Resistant Schizophrenia. *J Clin Psychiatry.* 2004;65:551-556.
[4] Volavka J, Czobor P, Sheitman B, et al. Clozapine, Olanzapine, Risperidone, and Haloperidol in the Treatment of Patients With Chronic Schizophrenia and Schizoaffective Disorder. *Am J Psychiatry*. 2002;159:255-262.

fails to mention that clozapine treatment should be discontinued if the QTc interval exceeds 500 msec.

Promotional materials are misleading if they fail to present risk information with a prominence and readability reasonably comparable to the presentation of information related to the effectiveness of the drug, taking into account all implementing factors such as typography, layout, contrast, headlines, paragraphing, white space, and any other techniques apt to achieve emphasis. Specifically, the four page article detailer prominently presents numerous efficacy claims throughout using colorful pictures and graphics, and large bolded headers, surrounded by a significant amount of white space. In contrast, the majority of the risk information is presented in smaller print, and in block paragraph format on the back page of the article detailer. The overall effect of this presentation undermines the communication of important risk information, minimizes the risks associated with clozapine, and misleadingly suggests that clozapine is safer than has been demonstrated. While we note the statement, "**Please see back cover for additional indications, Important Safety Information, and enclosed Prescribing Information, including Boxed Warnings**" (emphasis original), presented at the bottom of page three, this statement does not mitigate the misleading risk presentation.

By omitting and minimizing information regarding the serious risks associated with clozapine, the article detailer misleadingly suggests that clozapine is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Conclusion and Requested Action

For the reasons discussed above, the article detailer misbrands clozapine in violation of the FD&C Act, 21 U.S.C. 352(a) & 321(n), and FDA implementing regulation 21 CFR 1.21(a). *Cf.* 21 CFR 202.1 (e)(5)(i), (iii); (e)(6)(i), (ii); (e)(7)(i), (iii), (viii).

OPDP requests that Teva immediately cease the dissemination of violative promotional materials for clozapine such as those described above. Please submit a written response to this letter on or before April 22, 2013, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for clozapine that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA# 44 in addition to the ANDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for clozapine comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Jessica N. Cleck Derenick, PhD
Team Leader (Acting)
Office of Prescription Drug Promotion

{See appended electronic signature page}

Mathilda Fienkeng, PharmD
Team Leader (Acting)
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA N CLECK-DERENICK
04/08/2013

MATHILDA K FIENKENG
04/08/2013